

*Tinospora cordifolia* as an immunoadjuvant in conjunction with conventional antibacterial therapy.

One of the necessary elements for establishing a *prima facie* case of obviousness is that the prior art reference must teach or suggest all the claim limitations. *In re Vaack*, 947 F. 2d 488 (Fed. Cir.1991). Applicants respectfully submit that such a *prima facie* case of obviousness has not been established because the references cited do not disclose or suggest every feature claimed and there is no motivation for one of skill in the art to combine the references cited.

On page 2 of the Office Action, the rejection specifically refers to a portion (column 2, lines 25 – 40 in the “Background of the Invention”) indicating that Upadhyay et al. makes it clear that *Tinospora sp.* has been used in traditional Indian medicine for the treatment of urinary tract infection. The rejection further says that Upadhyay et al. discloses the ability of *Tinospora cordifolia* for use as an antibacterial, since it is reported to be protecting mice against *E. coli* induced abdominal sepsis. Further, on page 3 of the Office Action, the rejection indicates that Upadhyay et al. teaches that plants of the *Tinospora* species have been widely used in traditional Indian medicine for the treatment of urinary tract infections, which would include *Tinospora cordifolia*, since the plant is mentioned as a preferred plant in the genus of *Tinospora*.

Regarding De Souza et al. (US 2002/0142055), the rejection states that the reference teaches standardization of an extract of *Tinospora cordifolia* by bioassay and use of such a standardized extract for the administration of mammals. The rejection further says that De Souza et al. teaches that the extract is administered with a conventional therapy. On page 3 of the Office Action, the rejection makes reference to Example 5 and paragraph 48 of De Souza et al.

Prior to discussion of the disclosure of cited prior art references and their relevance to the instantly claimed invention, Applicants respectfully clarify that the instantly claimed invention does not relate to a method for the treatment of urinary tract infections (UTIs) or even the recurrent chronic UTIs using the standardized extract of *Tinospora cordifolia*, per se. Rather, the invention of independent claim I administers an effective amount of the standardized extract of *Tinospora cordifolia* as an immunoadjuvant, in conjunction with conventional antibacterial therapy (i.e. extract is used as an adjunct to conventional antibacterial therapy).

Applicants have demonstrated the efficacy of the present invention through the case study wherein the patients who were treated for recurrent UTI by administering a composition of the

standardized extract of *Tinospora cordifolia* as an adjunct with antibacterial therapy showed complete resolution over a one year observation period with no further episodes of UTI. See e.g. pages 16-19 and Tables in the present specification.

The prior art references cited in the Office Action provide no teaching or suggestion of the claimed invention, and there is no motivation to combine the references cited for at least the following reasons.

Upadhyay et al. only discusses general treatment of UTIs using plants of *Tinospora* species. However, the presently claimed invention is directed to a method of treating chronic recurrent UTIs using a specific species of *Tinospora* as an immunoadjuvant along with conventional antibacterial therapy. Upadhyay et al. is directed specifically to a method for ex vivo expansion of the number of hematopoietic cells for various clinical applications like transplantation of ex vivo expanded hematopoietic cells for restoration of immunocompetence, generation of activated and antigen sensitized immunocompetent cells for immunotherapy of cancer and infections, and ex vivo expansion of genetically transfected or transformed hematopoietic cells for gene therapy. Only in the Background of the Invention, is there a brief and general mentioning that plants of the *Tinospora* species have been widely used in traditional Indian medicine for treatment of skin infections, arthritis, fever, dysentery, urinary tract infections, and diabetes. However, there is no suggestion or teaching in Upadhyay et al. to use *Tinospora cordifolia* as an immunoadjuvant (i.e. adjunct), with conventional antibacterial therapy in the treatment of recurrent urinary tract infections.

With regard to the combined teachings of Upadhyay et al. and DeSouza et al., Applicants point out that Example 5 in De Souza et al., which is relied upon in the Office Action, is directed to use of the standardized extract as adjuvant therapy in patients with osteomyelitis. Moreover, the specification of De Souza et al. repeatedly refers to osteomyelitis, cancer, diabetes and respiratory system disorders as the diseases related to the immune system (see paragraphs [0022], [0023], [0024], [0025], [0033], [0034], [0035], [0036] and [0037]). Since osteomyelitis and urinary tract infections are clearly not related disorders, a person of ordinary skill in the art would not have looked at De Souza et al. for treating UTIs, and therefore would not have been motivated to use the extract of *Tinospora cordifolia* as an immunoadjuvant specifically for the treatment of recurrent urinary tract infection. At best, a person having ordinary skill in the art would look at the standardized extract of *Tinospora cordifolia* taught in De Souza et al. for use in

the culture medium of Upadhyay's method involving ex vivo expansion of the number of hematopoietic cells. Thus, there is no reasonable suggestion or motivation to one of skill in the art to combine the references cited and arrive at claim 1.

Moreover, Upadhyay et al. as noted above only generally mentions that the extract of the plants of *Tinospora* species may be useful in the treatment of UTIs. However, there is no suggestion that a person having ordinary skill in the art looking at the general disclosure of Upadhyay et al. would have considered its use as an immunoadjuvant. Further, even if it is known that a drug is effective against a disease, this does not necessarily suggest that it would be effective against the relapsing or recurrent form of the disease. Therefore it cannot be predicted, based on the references cited, that the extract of *Tinospora cordifolia*, when used as an adjunct therapy with conventional antibacterial therapy, would provide an effective treatment for chronic recurrent UTIs.

Therefore, the references fail to suggest use of a standardized extract of *Tinospora cordifolia* as an immunoadjuvant in conjunction with conventional antibacterial therapy for the treatment of a chronic recurrent urinary tract infection in a mammal. Claim 1 is not obvious over Upadhyay et al. and DeSouza et al. taken alone or in combination.

Further, concerning Applicants' previous citation of the abstract of Clin. Microbiol. Infect. 2004 Nov;10 Suppl 4:1-9 to establish long felt need, the rejection indicates that the article does not establish a long felt need, and says that Applicants have not proved long felt need for the treatment of antibacterial infections since they have been successfully treated.

Applicants first clarify that the previous response was not to establish long felt need for the general treatment of bacterial infections. Rather, the previous response was meant to establish long felt need for the treatment of recurrent UTIs. With reference to page 8, line 1 of the Office Action, namely the mentioned line "[o]ne article does not establish...long felt need", Applicants respectfully disagree with a conclusion that there is not a long felt need for the treatment of recurrent UTIs. Applicants respectfully submit herewith three additional references to further support the long felt need for the treatment of recurrent UTIs.

For at least the foregoing reasons, Applicants respectfully submit that claim 1 and the claims dependent therefrom are not obvious over the cited references alone or in combination.

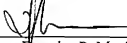
Regarding claim 15, claim 15 is directed to a method for the treatment of a renal disorder in a mammal suffering therefrom, consisting of administering to the mammal an amount effective for treating the renal disorder of a pharmaceutical composition consisting of a therapeutically effective amount of standardized extract of *Tinospora cordifolia* and a pharmaceutically acceptable carrier, in conjunction with conventional antibacterial therapy, wherein the renal disorder is a chronic recurrent urinary tract infection, both complicated and uncomplicated. Applicants respectfully submit that claim 15 and dependent claim 19 are also patentable over the references cited, for at least reasons similar to those discussed with respect to claim 1.

Favorable consideration is respectfully requested in the form of Notice of Allowance. If any questions arise regarding this communication, the Examiner is invited to contact Applicants' representative at the number listed below.

Respectfully submitted,

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